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Publication Date

2016-12-30

DOI

10.1016/j.pscychresns.2016.10.010

Peer reviewed

Psychiatry Research: Neuroimaging 258 (2016) 23–29

Contents lists available at ScienceDirect

Psychiatry Research Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

DTI microstructural abnormalities in adolescent siblings of patients with childhood-onset schizophrenia

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1. Introduction

Diffusion tensor imaging (DTI) is a non-invasive magnetic resonance imaging technique that provides information about the microstructural tissue architecture in different cerebral tissues in vivo. DTI measures the random molecular motion of water molecules (i.e. diffusion) by applying many diffusion-encoding gradients in different orientations (Beaulieu, 2002). DTI studies have demonstrated decreased white matter fractional anisotropy (FA) in adult onset schizophrenia (AOS) patients compared to healthy subjects (Camchong et al., 2009; Ellison-Wright and Bullmore, 2009; Hao et al., 2009; Hoptman et al., 2008; Munoz Maniega et al., 2008), though one study (Hoptman et al., 2008) showed an increase in FA.

Childhood onset schizophrenia (COS) is clinically continuous with the adult onset form of schizophrenia (Rapoport et al., 2005), in which psychosis develops before the age of 13. In addition, COS is a rare and more severe form of AOS and has a more pronounced genetic risk (Asarnow and Asarnow, 1994; Asarnow and Forsyth, 2013; Asarnow et al., 2001; Nicolson and Rapoport, 1999). There have been extremely few DTI studies in this population; Moran et al. (2015) and Clark et al. (2011) found decreased FA in COS patients, and Ashtari et al. (2007) found decreased FA in early onset schizophrenia (defined as onset before the age of 18) patients.

Since schizophrenia is a highly heritable disorder with a strong genetic disposition, studying non-affected relatives can reveal insights into the disorder without the confounding effects of medication. Gogtay et al. (2012) and Moran et al. (2015) found a delayed white matter growth trajectory and decreased FA in adolescent COS siblings, Boos et al. (2013) and Hoptman et al. (2008), found increased FA in adult first-degree relatives of AOS, while others (Harms et al., 2015; Koivukangas et al., 2015) found no differences in AOS relatives compared to controls.

Patients with schizophrenia and their first degree relatives also show substantial deficits in cognitive skill learning (Foerde et al., 2008; Gimenez et al., 2003; Purdon et al., 2003; Schroder et al., 1996; Wagshal et al., 2012; Weickert et al., 2010). The corticostriatal system plays an important role in skill learning (Knowlton et al., 1996; Poldrack and Gabrieli, 2001), suggesting that the pathophysiology of schizophrenia involves dysfunction of corticostriatal circuits (Buchanan et al., 1993; Buchsbaum, 1990; Kleist, 1960). One cognitive skill learning task that has been used extensively in the neuropsychological literature is the Weather Prediction Task (WPT) (Knowlton et al., 1994). The WPT requires participants to learn the probabilistic associations between visually presented cues and binary outcomes, followed by feedback as to whether they chose the correct outcome. Performance on the WPT is impaired in patients with schizophrenia (Foerde et al., 2008; Horan et al., 2008; Keri et al., 2005; Weickert et al., 2002) and their adult and adolescent relatives (Wagshal et al., 2012; Weickert et al., 2010). In addition, in previous fMRI and volumetric studies (Wagshal et al., 2015, 2013) examining a subset of these subjects, we have also demonstrated the COS siblings showed a relative deactivation in frontal and striatal regions, as well as in the cerebellum, compared to controls after extensive training on the WPT and that poorer performance in later learning on the WPT was related to a smaller volume in the cerebellum in COS siblings.

Taken together, the results from past studies support the idea that corticostriatal and cerebellar impairments in unaffected siblings of COS patients are behaviorally relevant and may reflect genetic risk for schizophrenia. Microstructural abnormalities may also play a role in the pathophysiology of schizophrenia and underlie some of the deficits experienced by relatives of schizophrenia patients as well. DTI is traditionally used for characterizing microstructural properties of white matter tracts, but has recently been employed in a novel way to detect microstructural abnormalities and overall cellular damage in subcortical gray matter regions as well (Bozzali et al., 2002; Cavallari et al., 2014; Caverzasi et al., 2014; Ciccarelli et al., 2001; Hannoun et al., 2012; Hasan et al., 2009, 2012, 2011; Muller et al., 2007; Piras et al., 2010; Spoletini et al., 2011; Vrenken et al., 2006). DTI can capture

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http://dx.doi.org/10.1016/j.pscychresns.2016.10.010
Received 29 April 2016; Received in revised form 25 October 2016; Accepted 28 October 2016
Available online 01 November 2016
0925-4927/ Published by Elsevier Ireland Ltd.

Table 1
Demographics of the COS siblings and all of the controls.

Variable	COS Siblings (n=13)		Controls (n=43)		P-value
	M	SD	M	SD	
Age	12.08	2.50	13.05	2.65	$p > 0.05$
Education	6.15	2.79	7.14	2.73	$p > 0.05$
Gender*	8/5		23/20		$p > 0.05$
Vocabulary**	45.17	8.81	59.35	10.21	$p < 0.001$ (Ctrl > Sibs)
Block Design***	44.50	9.52	56.00	8.41	$p < 0.001$ (Ctrl > Sibs)

* Males/Females.
** WASI Vocabulary subtest (missing 1 COS sibling).
*** WASI Block Design subtest (missing 1 COS sibling and 2 controls).

subtle changes in structure even before clinically measureable changes become apparent (Hulst et al., 2013).

Due to the conflicting results in the existing literature in patients with schizophrenia, and the fact that we were assessing adolescent relatives rather than adults, we tested a non-directional hypothesis that impairment in skill learning and altered network connectivity were related to alterations in microstructure. We employed DTI in a novel way to investigate abnormalities in gray matter regions, defined *a priori* based on the results of our past studies, as well as whole-brain white matter tracts. In a secondary analysis, we assessed the relationship between microstructural measures and WPT performance in adolescent siblings of COS patients and a group of control participants.

2. Methods

2.1. Participants

Thirteen adolescent siblings (age range: 8–16) of COS patients and forty-five adolescent controls (age range 8–18), who were right-handed and were matched in age, education, and gender to the COS siblings, participated in the study of microstructural differences across the brain (Table 1). An analysis was also conducted on a subset of these subjects (ten siblings of COS patients and forty-three controls) to investigate if these differences were related to WPT performance (accuracy). Behavioral data from the subjects in these analyses overlap with our previous studies describing group effects that used different neuroimaging modalities in siblings of COS patients (Wagshal et al., 2015, 2012, 2013).

The siblings of COS probands were recruited through previous participation in family studies of COS at the University of California, Los Angeles (UCLA). Families of potential control subjects who lived within a 25-mile radius of UCLA were identified by a survey research firm and were contacted by phone. All participants' parent or legal guardian provided informed consent while the participants themselves provided assent according to the procedures of the UCLA Institutional Review Board. Potential participants in both groups were screened and excluded for reports of prior treatments for psychiatric disorders including psychosis, attention-deficit hyperactivity disorder, learning disabilities, Tourette's Syndrome, traumatic brain injury, drug and alcohol abuse, other neurological disorders that affect cognitive functioning, or the presence of any psychotic symptoms. COS siblings were assessed by DSM-IV criteria using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1994) and did not have any psychotic symptoms or any schizophrenia spectrum diagnoses. Thus, in the present study, all subjects were free of clinical symptoms and were not taking medication for a psychiatric condition. Control subjects were also excluded if a first-degree relative had been reported to have been diagnosed with psychosis.

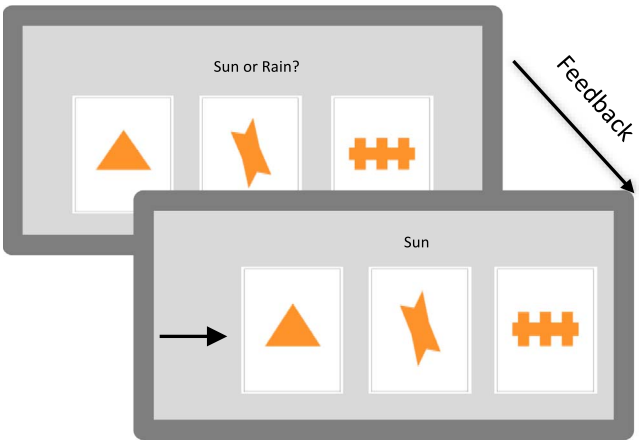

Fig. 1. The WPT task. Participants were told to predict the weather (sun or rain) based on cues. On every trial between 1 and 3 cues (out of 4 possibilities) could appear, yielding 14 possible combinations. The cues were probabilistically related to the outcomes. The association of the different cues with different probabilities was randomized across participants.

2.2. Task design and procedure

Participants were administered the WPT (Knowlton et al., 1994). The MATLAB (The MathWorks, Inc., Natick, MA) Psychophysics Toolbox (Brainard, 1997) version 7.4 was used to present the stimuli and to record responses on an Apple G4 PowerBook using the OSX operating system.

Subjects practiced the WPT (Fig. 1) for a total of one and a half hours, spanning two days. Participants were told to predict the weather (sun or rain) based on cues. On every trial between 1 and 3 cues (out of 4 possibilities) could appear, yielding 14 possible combinations. The cues were probabilistically related to the outcomes. The association of the different cues with different probabilities was randomized across participants. More details of the task are described elsewhere (Wagshal et al., 2012). On the first day, subjects were assessed for any neurological disorder or psychotic symptoms by a clinical psychologist and completed the Wechsler Abbreviated Scale of Intelligence (WASI) Vocabulary and Block Design subtests (Table 1). All subjects then completed 50 trials of the WPT inside an MRI scanner. On the second day, all subjects were trained for an additional 800 trials outside the scanner occurring in two sets with an intervening break of 30 min where a sensorimotor task (the serial reaction time task) was performed. Subjects then completed an additional 50 trials of the WPT inside an MRI scanner.

2.3. Imaging procedure

Scanning was performed on a 3-Tesla Siemens Allegra head-only MRI scanner in the Ahmanson-Lovelace Brain Mapping Center at UCLA. A structural image consisting of a magnetization-prepared rapid acquisition gradient echo image (MPRage) was collected: sagittal slices; slice thickness, 1 mm; TR=2300 ms; TE=2.1 ms; voxel size=1.3×1.3×1.0 mm; 0.5 mm gap; flip angle=8°; matrix, 192×192; field of view=256. For the DTI paradigm, diffusion gradients were applied in 35 directions uniformly distributed with b_0=800 s/mm^2. The DTI images consisted of a 2.5×2.5×2.5 voxel size, slice thickness=2.5 mm, TR=7300 ms, TE=95 ms, and 5 b_0 images.

2.4. DTI metrics

Fractional anisotropy (FA), which quantifies the directionality of diffusion, is a fairly non-specific biomarker of microstructural architecture and neuropathology and can be regarded as a summary measure for microstructural features of the nerve fibers (Alexander

et al., 2011, 2007). Mean diffusivity (MD) measures the average diffusion in all directions and represents isotropic diffusivity, which provides information about changes in the interstitial space and is sensitive to cellular damage (e.g. edema and necrosis) (Alexander et al., 2011; Basser, 1995). More neurobiological specificity is available from two directional diffusivities: axial diffusivity (AD), which measures diffusion parallel to the axonal fibers and is correlated with axonal pruning (Bockhorst et al., 2008; Budde et al., 2009), while radial diffusivity (RD), measures diffusion perpendicular to the fibers and is related to myelin injury or decreased myelination (Song et al., 2003, 2002). Typically, FA and MD are inversely related, while the direction of RD and AD vary (Alexander et al., 2007). Lower levels of FA and higher levels of MD are typically associated with decreased directionality and density of white matter.

2.5. DTI processing and analysis

Data processing was conducted using (FMRIB) Software Library (FSL) version 5.0.8 and FMRIB's Diffusion Toolbox (FDT) (Smith et al., 2004). Head motion and eddy current induced distortions were corrected through affine registration of the diffusion-weighted images to the first B0 image using the "eddy_correct" tool. Motion artifacts were inspected and subjects with greater than 3 mm of relative movement were excluded. Two control subjects were excluded from the analysis due to motion. The gradient directions were corrected according to the rotation parameters. Then a diffusion tensor model was fit to the raw diffusion data at each voxel to get DTI derived metrics (i.e. FA, MD, RD, and AD) using weighted least squares.

2.5.1. DTI gray matter ROI processing

All subjects' DTI data were then aligned into a common space via a structural scan. Transformation matrices were obtained using the FSL linear registration tool FLIRT and the nonlinear registration tool FNIRT (Andersson et al., 2007a, 2007b), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). Next, based on an *a priori* hypothesis of regions that are involved in the WPT task based on our previous fMRI data, 4 bilateral standard space ROIs were anatomically defined from the FSL Harvard-Oxford atlas; these ROIs included the bilateral putamen, caudate, anterior PFC, and paracingulate gyrus. MD metrics from these gray matter ROIs were obtained and used in the analysis and FDR corrected for multiple comparisons.

2.5.2. DTI TBSS processing

Voxel-wise statistical analysis of the FA data was carried out using Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006) in FSL 5.08. TBSS projects all subjects' FA data onto a mean FA tract skeleton, before applying voxelwise cross-subject statistics thresholded at $p < 0.05$ and correcting for multiple comparisons (i.e. family-wise error). This same process was done to also generate the other DTI metrics.

2.6. Statistical data analysis

Data were analyzed using SPSS (V.21, SPSS, Chicago) and R (www.r-project.org). Independent subjects *t*-tests were performed to analyze group differences in age, education, and IQ (WASI Vocabulary and Block Design subtests). A chi-squared test was used to examine gender differences between the groups. Performance (accuracy) on the WPT was analyzed early in learning (first 50 trials on Day 1) and late in learning (trials 751–800) when performance was at asymptotic levels in control subjects. Three siblings of COS patients were excluded from the WPT analysis due to lack of behavioral data (computer malfunction, not responding on more than 10% of the WPT trials, or not completing both days of WPT training). In addition, independent subjects' *t*-tests were performed to analyze group differences in DTI MD gray matter ROIs and correlations between MD measures and WPT performance applying a Bonferroni correction.

3. Results

3.1. Behavioral results

Similar to past results of studies of first-degree relatives of patients with schizophrenia, the COS siblings had significantly lower scores on two WASI subscales (Vocabulary, $t(53)=4.373$, $p < 0.001$, and Block Design, $t(51)=4.045$, $p < 0.001$) than controls. One COS sibling was not tested on the Vocabulary subtest, and one COS sibling and two control participants were not tested on the Block Design subtest due to time constraints. We also conducted a correlation analysis to determine if IQ was related to WPT performance. For the COS sibling group, there was no relationship between scores on the Block Design or Vocabulary subtests of the WASI and either early or late WPT performance (all *p*'s > 0.05) (Table 1). For the controls, there was a modest correlation between the Vocabulary subtest and late WPT performance, $r(32)=0.358$, $p=0.044$. No other correlations were significant.

3.2. DTI MD gray matter ROI results

We examined mean diffusivity microstructural DTI gray matter ROI differences between the groups. We found group differences for the putamen, $t(54)=2.676$, $p=0.040$, with the controls having a higher value than the COS siblings (Fig. 2). While both groups were matched in age and gender, we also added these variables as covariates since these variables are known to correlate with gray matter. The results paralleled the main analysis for the controls to have a higher value than the COS siblings, $F(1, 52)=6.160$, $p=0.016$. In addition, none of the interactions were significant. For clarity, we also demonstrate the relationship between age and group for the putamen (Fig. 3).

We then conducted an analysis to determine if MD differences between the groups were related to average WPT performance as well as separate analyses for early and late WPT learning. There were no significant correlations for either group.

3.3. DTI TBSS results

We examined white matter DTI differences between the groups throughout the entire brain and found widespread tracts in which the COS siblings displayed decreased MD, RD, and AD in white matter structure compared to controls (Fig. 4 and Supplementary materials Table 2). While both groups were matched in age and gender, we also

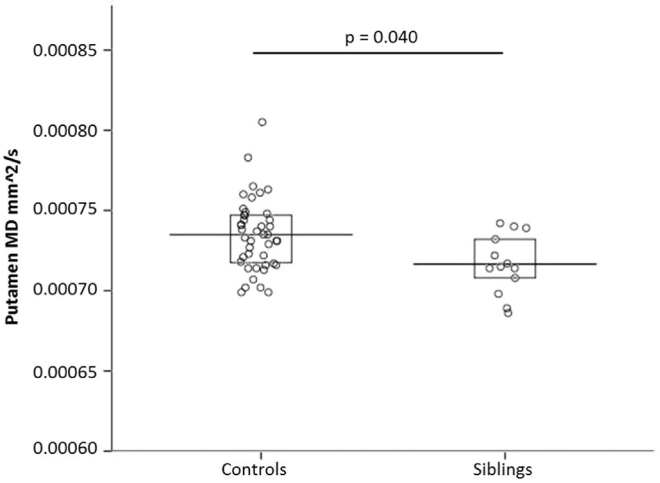

Fig. 2. DTI Gray Matter ROI for the bilateral putamen. There was a significant difference between the groups with the COS siblings having reduced MD compared to controls, $p=0.040$.

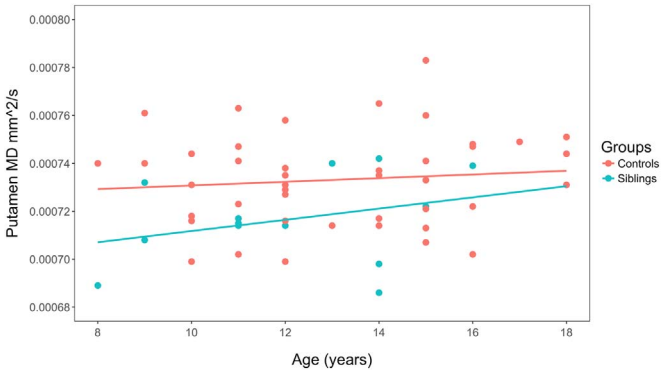

Fig. 3. Scatterplot for Group x Age Interaction for the bilateral putamen. There was no significant interaction between the groups.

added these variables as covariates since these variables are known to correlate with white matter. The pattern of results mirrored the original analysis.

As a secondary analysis, we wanted to determine if white matter differences between the groups were related to early or late WPT performance (Supplementary materials Tables 3 and 4). In the COS siblings, there was a negative correlation with early WPT learning and overall FA and positive correlations with overall MD and RD. There was also a significant positive correlation with early WPT learning and AD in the body and genu of the corpus callosum in the COS siblings (Fig. 5). In addition, asymptotic WPT performance was positively correlated with AD in the COS siblings in the right inferior longitudinal fasciculus, bilateral inferior fronto-occipital fasciculus, and bilateral cerebellum. There were no significant correlations between FA measures and performance in the controls.

4. Discussion

To our knowledge, this is the first study to examine microstructural alterations in both white and gray matter in adolescent siblings of COS patients and adds more information to previous literature in focusing on adult relatives of patients with adult-onset schizophrenia. Overall, our study found evidence of a decrease in measures of gray and white matter diffusivity in COS siblings compared to controls. We demonstrated a reduction in MD in the putamen in COS siblings compared to controls. This reduction may indicate abnormal connectivity or increased packing of neurons (Alexander et al., 2011; Basser, 1995). We also found widespread *decreases* in white matter MD, RD, and AD throughout the brain in the COS siblings compared to controls. In relation to cognitive skill learning, the overall increase in white matter FA was associated with poorer WPT performance in COS siblings. However, some measures of white matter structural alterations in COS siblings may be compensatory; increased overall MD and RD in this group were related to better learning in the WPT. In striatal ROIs that have been associated with learning in the WPT, siblings of COS patients showed reduced MD, which may contribute to performance deficits in this group.

While the majority of studies investigating first-degree relatives of schizophrenia patients have revealed decreasing FA in tracts compared to controls (Camchong et al., 2009; Hao et al., 2009; Hoptman et al., 2008; Munoz Maniega et al., 2008), there have been a few studies that have demonstrated increased FA (Boos et al., 2013; Hoptman et al., 2008). One possible explanation for the difference is that previous studies have examined adult relatives of patients with schizophrenia, while the present study tested adolescent relatives. Thus, the results of the present study may reflect differences in the developmental trajectory of COS relatives and controls in terms of white matter microstructure. In addition, there may be differences between first-degree relatives of patients with adult onset and childhood onset schizophrenia. Siblings of COS patients have stronger genetic vulnerability to develop schizophrenia compared to relatives of adult onset schizo-

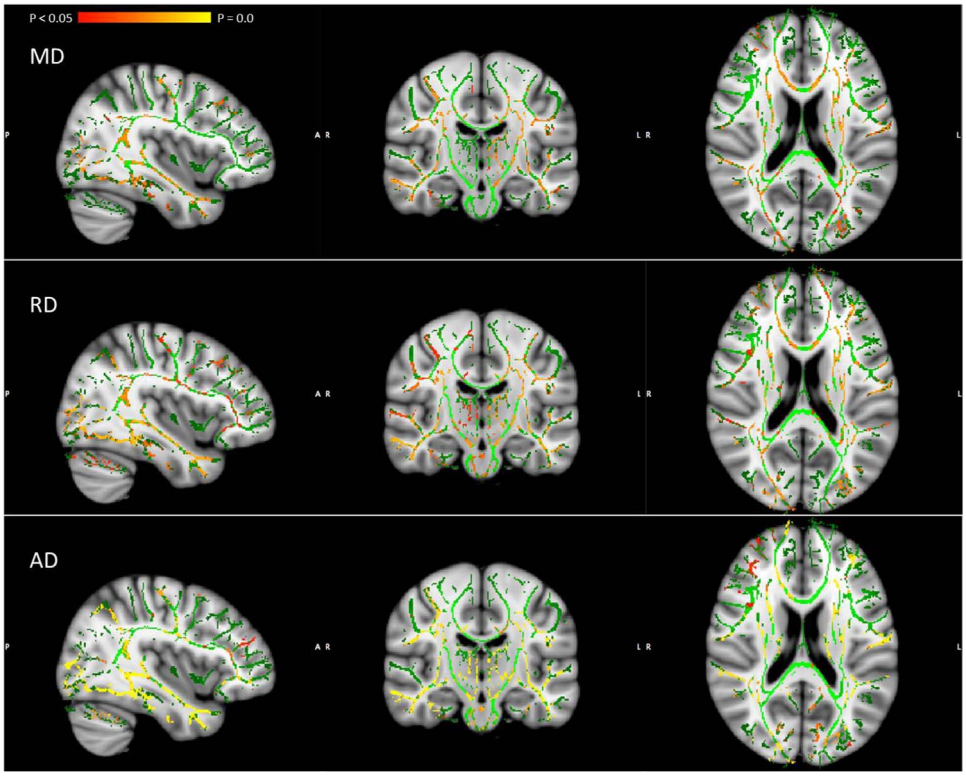

Fig. 4. DTI TBSS results. There are widespread tracts in which the COS siblings display differences in white matter microstructure as measured by decreased MD, RD, and AD compared to controls. FWE p-value < 0.05. Green indicates the skeleton template.

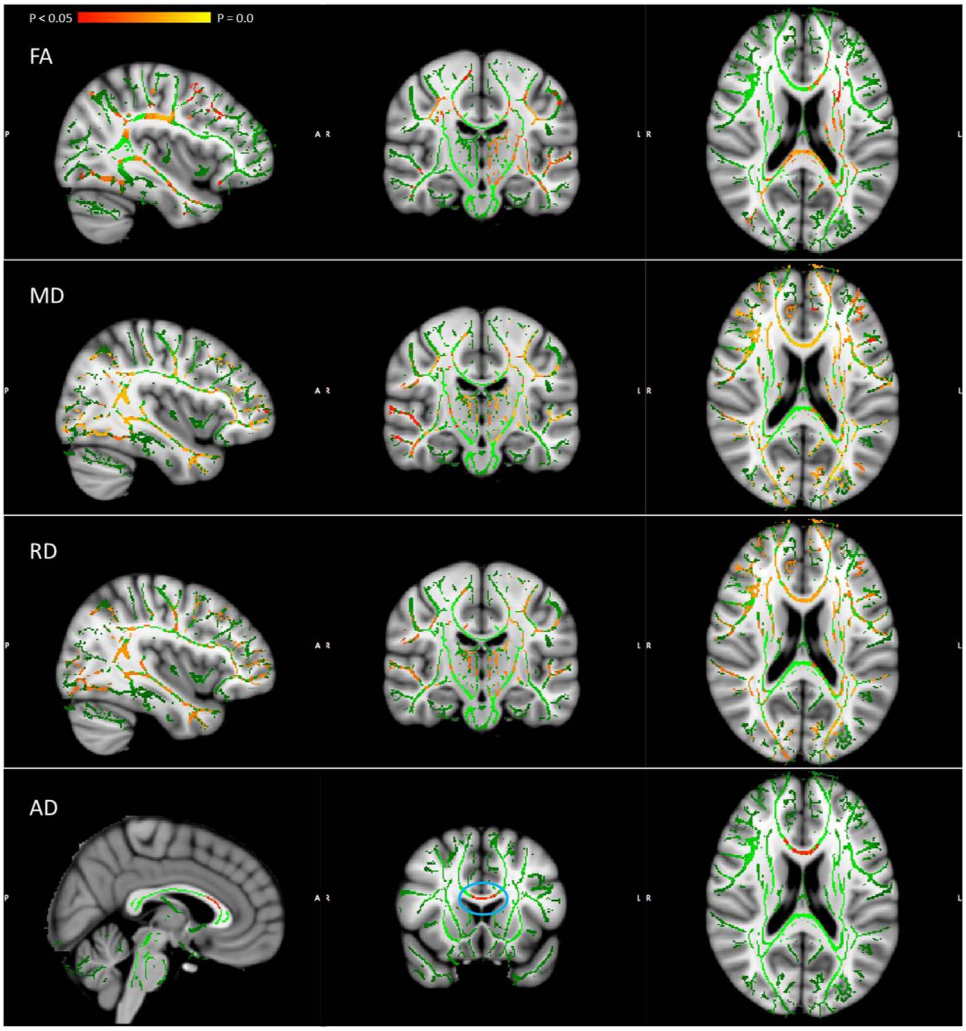

Fig. 5. DTI TBSS results. Negative correlation with early WPT learning and overall FA in siblings of COS patients; positive correlations with MD and RD; positive correlation with early WPT learning and AD in the body and genu of the corpus callosum in the COS siblings. FWE p-value < 0.05. Green indicates the skeleton template.

phrenia.

One reason for greater white matter FA in COS siblings could be progressive gray matter loss during adolescence (Cannon et al., 2015; Gogtay et al., 2007; Wagshal et al., 2015), which could reflect abnormalities in synaptic pruning (Glausier and Lewis, 2013; Sekar et al., 2016) or an increase in myelinated white matter (Boos et al., 2013). Some of the white matter microstuctural changes that were present in the COS siblings may be compensatory, as RD and MD were positively related to learning on the WPT task in the COS siblings. Moreover, age may be a factor in the findings of a decrease in white matter in patients with schizophrenia and their relatives, as studies have found that white matter directionality decreases with increasing age and in patients with illness chronicity (Boos et al., 2013; Kochunov et al., 2013; Kubicki et al., 2002; Maddah et al., 2008; Mandl et al., 2010; Rosenberger et al., 2008). Thus, the deficit in white matter directionality that has been found in adult relatives of patients with schizophrenia may reflect an increased rate of loss of white matter integrity which is not yet apparent in the adolescent relatives of COS patients. There is also some preliminary evidence from a longitudinal study of siblings of COS patients that white matter growth is abnormal during development but normalizes with age (Gogtay et al., 2012).

The existing literature suggests that white matter microstructural abnormalities may be markers of genetic risk for schizophrenia, and furthermore, that the trajectory of white matter development may be different in individuals with genetic risk for schizophrenia. There is increasing evidence that the pathophysiology of schizophrenia results from abnormal connectivity or communication (Friston and Frith, 1995; McGuire and Frith, 1996; Olabi et al., 2011). Studying relatives of COS patients may give insight into the neurodevelopmental trajectory of schizophrenia due to the greater genetic risk. Ultimately, more longitudinal studies in relatives of COS patients are needed in order to shed light on the relevance of changes in gray and white matter microstructure, the development of schizophrenia, and the cognitive skill learning deficits associated with this population.

Funding

This work was supported by the Della Martin Foundation and a National Institute of Mental Health grant (MH 72697).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.pscychresns.2016.10.010.

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